UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/621,803	07/17/2003	Kenneth A. Browne	GP131-03.UT	5941

21365 7590 10/10/2008

GEN PROBE INCORPORATED
10210 GENETIC CENTER DRIVE
Mail Stop #1 / Patent Dept.
SAN DIEGO, CA 92121

EXAMINER	
STRZELECKA, TERESA E	

ART UNIT	PAPER NUMBER
1637	

NOTIFICATION DATE	DELIVERY MODE
10/10/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentdept@gen-probe.com
kelleec@gen-probe.com
belindao@gen-probe.com

Office Action Summary	Application No.	Applicant(s)	
	10/621,803	BROWNE, KENNETH A.	
	Examiner	Art Unit	
	TERESA E. STRZELECKA	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 August 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *44-52 and 55* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *44-52 and 55* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on August 25, 2008 has been entered.

2. Claims 44-52 and 54 were previously pending. Applicant amended claim 44, cancelled claim 54 and added new claim 55. Claims 44-52 and 55 will be examined.

3. Applicant's cancellation of claim 54 overcame the rejection of this claim under 35 U.S.C. 103(a) over Adams, Hanninen, Mueller and Majlessi. All other previously presented rejections are withdrawn. New grounds for rejection are presented in this office action, therefore Applicant's arguments are moot.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 44-48, 50-52 and 55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ohyama et al. (Biotechniques, vol. 29, pp. 530-536, 2000) as evidenced by Wodicka et al. (Nat. Biotechnol., vol. 15, pp. 1359-1367, 1997), Marble et al. (Biotechnol. Prog., vol. 11, pp. 393-396, 1995; cited in the IDS), Adams et al. (U.S. patent No. 6,060,288 A; cited in the previous office action), Hanninen et al. (U. S. Patent No. 6,310,354 B1; cited in the previous office action) and

Majlessi et al. (Nucl. Acids Res., vol. 26, pp. 2224-2229, 1998; cited in the IDS and in the previous office action).

A) Regarding claim 44, Ohyama et al. teach a device for detecting a target nucleic acid, the device comprising:

a solid support having a surface (Ohyama et al. teach a device for detection of RNA by hybridization comprising solid support in the form of oligonucleotide array (page 532, last paragraph; page 533; Fig. 3).);

an amplification primer comprising a promoter sequence for an RNA polymerase and a sequence complementary to a first strand of said target nucleic acid (Ohyama et al. teach an amplification primer comprising an RNA polymerase promoter, the primer being complementary to a target nucleic acid (page 532, paragraphs 2-4)).; and

a hybridization probe separate from the amplification primer immobilized to said surface, wherein said hybridization probe comprises a sequence complementary to an amplicon synthesized using said amplification primer and said target nucleic acid as a template in a nucleic acid amplification reaction (Ohyama et al. teach hybridization of labeled RNA targets to the immobilized probes (page 532, last paragraph; page 533; Fig. 3).).

Regarding claim 45, Ohyama et al. teach arrays prepared by the method of Wodicka et al. (page 533, second paragraph). As evidenced by Wodicka et al., the arrays were prepared on glass substrates or chips (page 1366, first paragraph).

Regarding claims 47 and 48, Ohyama et al. teach arrays prepared by the method of Wodicka et al. (page 533, second paragraph). As evidenced by Wodicka et al., the arrays were prepared by directly synthesizing oligonucleotides on glass substrates or chips (page 1365, last paragraph; page

1366, first paragraph), therefore they inherently teach probes covalently immobilized to the substrate.

Regarding claim 50, Ohyama et al. teach arrays prepared by the method of Wodicka et al. (page 533, second paragraph). As evidenced by Wodicka et al., the arrays were prepared using 260,000 oligonucleotide probes, therefore they teach at least two different probes (Abstract; page 1365, last paragraph).

Regarding claim 55, Ohyama et al. teach the device in contact with RNA amplification products which are not immobilized on the surface of the support (page 532, fifth paragraph).

B) Regarding claims 44-48, 50-52 and 55, Ohyama et al. do not teach amplification of RNA using primers immobilized onto beads.

C) Marble et al. teach amplification of RNA in solution using primers comprising a promoter for RNA polymerase immobilized onto agarose beads (Abstract; Fig. 1; page 393, last paragraph; page 394, paragraphs 1-6).

It would have been *prima facie* obvious to one of ordinary skill in the art to have used the immobilized RNA polymerase promoter-primer of Marble et al. in the method of RNA detection by hybridization of Ohyama et al. The motivation to do is provided by Marble et al. (page 396, last paragraph):

"Solid-phase templates sustain T7 RNA polymerase transcription to an extent similar to that of DNA templates in free solution, when compared under standard reaction conditions. Unlike solution-phase DNA, immobilized DNA is easily recovered from the crude transcription reaction mixture for subsequent reuse. DNA removal simplifies the composition of the reaction mixture, ultimately facilitating its purification. Most importantly, support-bound templates show only gradual reduction in activity through multiple cycles of transcription, thereby increasing the overall

RNA yield from the templates. Transcriptional activity after many rounds may be partially restored by the addition of fresh coding-strand DNA. Together, these results suggest that immobilized templates are particularly useful for large-scale transcription applications, including continuous-flow and semibatch bioreactor designs."

D) Neither Ohyama et al. nor Marble et al. teach both primer and probe immobilized onto the same support, or probes labeled before contacting with polymerase.

E) Regarding claim 44, Adams et al. teach a device for detecting a target nucleic acid, the device comprising:

a solid support bead having a surface (Adams et al. teach a device for amplifying nucleic acids comprising beads (Fig. 1; col. 6, lines 65-67; col. 7, lines 41, 42).);

an amplification primer immobilized to the surface of said solid support bead, said amplification primer comprising a promoter sequence for an RNA polymerase and a sequence complementary to a first strand of said target nucleic acid (Adams et al. teach an amplification primer immobilized to the beads, the primer being complementary to a target nucleic acid (Fig. 1; col. 2, lines 4-25; col. 3, lines 41-62).; and

a labeled hybridization probe separate from the amplification primer immobilized to said surface,

wherein said labeled hybridization probe comprises a sequence complementary to an amplicon synthesized using said amplification primer and said target nucleic acid as a template in a nucleic acid amplification reaction, and

wherein prior to contact of said device with any nucleotide polymerizing enzyme said labeled hybridization probe comprises a detectable label and is immobilized to said surface (Adams et al. teach detection of the amplicons with labeled hybridization probes (col. 4, lines 57-67); col.

13, lines 8-16). Therefore, since the probe is hybridized to an immobilized amplicon, the probe is itself immobilized, according to Applicant's definition. The probe is labeled independently of the polymerization reaction being performed.).

Regarding claim 45, Adams et al. teach glass and plastic (col. 7, lines 45-51; col. 14, lines 36-44).

Regarding claims 46-48, Adams et al. teach covalent immobilization of primers (col. 2, lines 1-3).

Regarding claim 50, Adams et al. teach multiplex detection of different targets using primers with different sequences (col. 5, lines 3-13).

Regarding claims 51 and 52, Adams et al. teach immobilization of a single primer on the solid support (col. 2, lines 1-63; col. 5, lines 7-9; col. 22, lines 48-56; col. 23, lines 19-26).

F) Adams et al. probes binding to an immobilized amplicon, but do not teach immobilized labeled probes.

G) Hanninen et al. teach a method of detection of PCR amplification using different combinations of immobilized primers and/or primers and probe, and they teach immobilized labeled fluorescent probes (col. 4, lines 23-33, 39-63; col. 5, lines 5-10 and 35-41; col. 6, lines 59-67; col. 7, lines 1-5).

Therefore it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used immobilized labeled probe of Hanninen et al. together with immobilized primers of Adams et al. in the method of RNA detection of Ohyama et al. and Marble et al. with a reasonable expectation of success. The motivation to do so is provided by Adams et al., who stated (col. 3, lines 41-62):

"In another embodiment of the present invention, a pair of oligonucleotides is immobilized on the solid support. For example, a pair of oligonucleotide primers (e.g., primer (a) and primer (b)) can be used, with the nucleotide sequence of each primer complementary to a different region of the target nucleic acid sequence. Typically the different regions of the target sequence are at opposite ends of the target sequence. During the annealing step of the amplification reaction, a single-stranded target nucleic acid molecule, which has been formed by the elongation of primer (a), comprises a region of sequence (b) at the opposite end of the strand. Because this single-stranded target sequence is still immobilized on the solid support, and if a second primer is present on the solid support with a sequence complementary to sequence (b), the end of this target sequence will anneal to primer b, and a target molecule will form that is attached to the solid support at both ends. This molecule essentially forms a "bridge" between primer (a) and primer (b). Thus, multiple target sequences can be readily detected simultaneously because the amplification products are "captured" on the support and cannot dissociate back into solution and possibly escape detection."

Therefore, since the second primer of Adams is really an unlabeled probe to which the amplified first strand binds, having a labeled probe in the vicinity of the amplification primer would allow instant detection of the amplified fragment, since it would bind to the probe, rather than dissociating into solution.

H) None of the above references teach probes comprising 2'-methoxy nucleotide analogs.

I) Majlessi et al. teach probes comprising 2'-methoxy nucleotide analogs (Abstract) and their use in detection of RNA targets (page 2228, last two paragraphs; page 2229; Fig. 3).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used the 2'-methoxy nucleotide analogs of Majlessi et al. as the fluorescent probes in the method of Ohyama et al., Marble et al., Adams et al. and Hanninen et al. with a

reasonable expectation of success. The motivation to do so, provided by Majlessi et al., would have been, as stated by Majlessi et al. (page 2229, last paragraph):

"In summary, 2'-*O*-methyl oligoribonucleotide probes afford multiple advantages over 2'-deoxy oligoribonucleotide probes for detecting RNA targets, including greatly increased *T*m, which allows use of shorter probes, faster kinetics of hybridization, ability to bind to structured targets under conditions where 2'-deoxy oligoribonucleotide probes will not and significantly improved specificity. These advantages render 2'-*O*-methyl oligoribonucleotide probes superior to 2'-deoxy oligoribonucleotide probes for use in assays that detect RNA targets."

6. Claim 49 is rejected under 35 U.S.C. 103(a) as being unpatentable over Ohyama et al. (Biotechniques, vol. 29, pp. 530-536, 2000) as evidenced by Wodicka et al. (Nat. Biotechnol., vol. 15, pp. 1359-1367, 1997), Marble et al. (Biotechnol. Prog., vol. 11, pp. 393-396, 1995; cited in the IDS), Adams et al. (U.S. patent No. 6,060,288 A; cited in the previous office action), Hanninen et al. (U. S. Patent No. 6,310,354 B1; cited in the previous office action) and Majlessi et al. (Nucl. Acids Res., vol. 26, pp. 2224-2229, 1998; cited in the IDS and in the previous office action), as applied to claim 44 above, and further in view of Fang et al. (J. Am. Chem. Soc., vol. 121, pp. 2921-2922, 1999; cited in the IDS and in the previous office action).

A) The teachings of Ohyama et al., Marble et al., Adams et al., Hanninen et al. and Majlessi et al. are presented above. Regarding claim 49, Hanninen et al. teach fluorescently labeled probes, but do not teach probes comprising fluorophore and a quencher.

B) Regarding claim 49, Fang et al. teach detection of nucleic acid targets using molecular beacons immobilized to a solid surface (page 2922, paragraphs 2 and 4-6).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used the molecular beacons of Fang et al. as the fluorescent probes in the method

of Ohyama et al., Marble et al., Adams et al., Hanninen et al. and Majlessi et al. with a reasonable expectation of success. The motivation to do so, provided by Fang et al., would have been, as stated by Fang et al. (page 2921, first paragraph and page 2922, fifth paragraph):

"MBs have extremely high selectivity with single base pair mismatch identification capability. They hold great promise for studies in genetics, disease mechanisms, and molecular interactions, for applications in disease diagnostics, and in new drug development."

"Our results indicate the MB-immobilized plate can be used to detect target DNA molecules in the subnanomolar range. In addition, preliminary experiments have shown that the immobilized DNA molecules on the plate can be regenerated after hybridization. Therefore, we will be able to reuse the plate multiple times for DNA detection and interaction studies."

Therefore, the molecular beacons of Fang et al. are an alternative to probes of Ohyama et al. for the detection of nucleic acid targets with high specificity.

7. No claims are allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TERESA E. STRZELECKA whose telephone number is (571)272-0789. The examiner can normally be reached on M-F (8:30-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Teresa E Strzelecka
Primary Examiner
Art Unit 1637

/Teresa E Strzelecka/
Primary Examiner, Art Unit 1637
September 30, 2008